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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

CONTINUATION SHEET:

Continuation of 5. Applicant's reply has overcome the following rejection(s): all rejections of claims 68-76 are rendered moot by their cancellation

Continuation of 11: Applicants have traversed the rejection of claims 59-67 and 77 over Shum-Tim et al, in light of Henrikson, in view of Dunkelman et al, Mitchell et al and Hall et al.

First Applicants assert Shum-Tim et al does not disclose applying the cells and matrix to the <u>outside</u> of a tubular support, nor does Shum-Tim et al teach or suggest a <u>porous</u> tubular support, as Shum-Tim et al does not disclose applying cells to the PHA outer component of the device, nor is the PHA porous.

Second, Applicants traverse the holding of obviousness that it would have been obvious to apply the cell-seeded polymer scaffold (cells and matrix) of Shum-Tim to the porous tubular support of Dunkelman for the seven day culture period on the grounds that altering the Shum-Tim procedure by layering the seeded graft around the Dunkelman porous tube would have interfered with the effective functioning of the Shum-Tim method. Specifically, because the seven-day culture period (of Shum-Tim) is disclosed as necessary for attachment of the cells to the scaffold, Applicants assert that manipulation of the cell-seeded scaffold prior to the conclusion of the seven day culture period, including manipulation to place the cell-seeded scaffold onto the Dunkelman apparatus, and particularly operation of the Dunkelman apparatus, would result in displacement of the yet-non-adhered cells. As such, Applicants assert that one would not have been motivated to modify the method of Shum-Tim as suggested by the Examiner, nor would one have had a reasonable expectation that such a modification would be successful. Finally, Applicants assert that the proposed modification would not result in the claimed method (particularly step (b) of claim 77), which requires growing the endothelial cells, smooth muscle cells and

matrix on the exterior surface of the tubular support because the cells would be lost in the Dunkelman apparatus.

In response to Applicants' first argument, it is respectfully submitted that the rejection of record does not assert that cells are applied to the outside of the PHA component of the device of Shum-Tim et al, rather the rejection of record is based on the fact that Shum-Tim et al apply the cells to the *inner* PGA polymer scaffold of the device of Shum-Tim et al, wherein the PGA polymer scaffold is considered to read on at least one component of the "matrix" of the instant invention, and then that it would have been *prima facie* obvious to apply the cell-seeded PGA scaffold (cells and matrix) into the culture apparatus of Dunkelman, which would involve circumferentially positioning the cells and matrix around the porous tubular support of the device of Dunkelman.

In response to Applicants' second argument, it is respectfully submitted that Dunkelman disclose that vascular grafts may be both seeded and cultured within the disclosed apparatus; Dunkelman specifically claim a method for seeding and culturing a tubular prosthesis (See Dunkelman claims 56-61). It is submitted that one having ordinary skill in the art would have been able to readily determine the appropriate amount of time required between the actual seeding of the cells onto the scaffold and beginning of aggressive pumping of fluid through the lumen. One having ordinary skill in the art will understand that while cells do not instantaneously adhere to substrates, within a matter of hours cells would be expected to have established sufficient attachment so as to operation of the device of Dunkelman. The fact that the method of seeding and culturing cells is claimed in the patent of Dunkelman (claim 56) means that one having ordinary skill in the art, as of 1996 (the filing date of Dunkelman) would have been able to successfully carry out the method of seeding and culturing a vascular graft within the apparatus of Dunkelman without dislodging all cells from the scaffold.

Therefore, the arguments are not found persuasive; it is maintained that one would have been motivated to modify the method of Shum-Tim et al to involve seeding and culturing of the scaffold within the device of Dunkelman, for the purpose of providing an improved vascular graft, in that the graft was cultured under dynamic conditions, which result in pre-conditioning of the graft, and desired cell alignment within the graft. Furthermore, one would have had a reasonable expectation of successfully seeding and culturing the graft of Shum-Tim within the device of Dunkelman because Dunkelman disclose that their apparatus can successfully carry out methods of seeding and culturing vascular graft prosthesis. Thus the invention as a whole is maintained as *prima facie* obvious over the cited references.

Claims 59-67 and 77 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shum-Tim et al (Ann Thorac Surg, 1999), in light of Henrikson (Ed.) (Histology, 1999), and taken in view of Dunkelman et al (US Patent 5,792,603), and further in view of Mitchell et al (Cardiovascular Pathol, 2003) and Hall et al (US Patent 6,387,663).

Shum-Tim et al disclose development of tissue-engineered vascular graft comprising seeding a mixture of endothelial cells, smooth muscle cells and fibroblasts onto a polymeric scaffold. The cells are cultured on the scaffold for seven days, and then implanted as an aortic replacements (See Shum-Tim et al, Pg. 2298-2299 "Materials and Methods: Cell Isolation").

In the method of Shum-Tim et al the polymeric scaffold is considered to read on the matrix of the claimed invention. The cells are seeded onto the matrix as a mixed population, thus none of the cells are cultured on the matrix or contacted with any growth factors prior to all cells being present on the matrix.

Smooth muscle cells naturally secrete type IV collagen (See Henrikson et al, Histology, page 98); thus, upon culture the smooth muscle cells secrete collagen into the matrix, and thus the matrix further comprises collagen.

The source of the cells, as recited by claims 60-64, are submitted to be product-by-process limitations. As discussed previously, product-by-process limitations are considered only insofar as the method of production (or in the instant case, the original source of the cells) imparts distinct structural characteristics or properties to the product being claimed (in the instant case, the ECs and SMCs used in the blood vessel). In the instant case, requiring the ECs and SMCs to be *derived* from stem cells does not impart any structural distinction to the adult ECs or SMCs; in fact, it is submitted all cells are ultimately *derived* from stem cells. Therefore, the source of the cells does not differentiate over the teachings of Shum-Tim et al, and claims 60-64 are properly included in the rejection of record.

Shum-Tim et al differs from the instant invention in that they do not disclose details of the seven day culture period which occurs after cell seeding and before implantation of the tissue-engineered vascular graft. Specifically, Shum-Tim et al do not disclose circumferentially positioning the cell-seeded matrix around a tubular support, through which one or more factors are contained, and culturing thereupon.

Dunkelman et al disclose an apparatus for producing a vascular graft comprising a perfusion system which includes a porous tube (48) onto which a vascular graft may be circumferentially positioned around; perfusate is circulated through the system, and specifically through the porous tube (48); the porous tube permits transfer of the perfusate from within the tube to the vascular graft to achieve culture of the vascular graft. The porous tube (48) may be comprised of a porous polymer, such as PTFE (Teflon), PVC, or polycarbonate (porous plastics). (See Dunkelman et al, col. 4, ln 54-col. 5, ln 21). By altering the pressure with which the perfusate is pumped through the system, the porous tube is caused to controllably expand and contract, which places a varying radial stress on the vascular graft scaffolding, which simulates physiological conditions (See Dunkelman, col. 4, ln 26-31) and encourages a desired alignment of cells on the scaffold (See Dunkelman, claim 56). In this manner the vascular graft produced

within the apparatus of Dunkelman has improved properties over vascular grafts which have not been exposed to such dynamic conditioning. The graft may be seeded and cultured directly within the apparatus of Dunkelman using means well known in the art (See Dunkelman, col. 7, ln 62-col. 8, ln 7 & claims 56-61).

It is submitted that one of ordinary skill in the art would have found it *prima facie* obvious to modify the method of Shum-Tim such that the vascular graft of Shum-Tim et al is produced within the apparatus of Dunkelman et al. Dunkelman et al clearly state that a vascular prosthesis may be provided within their apparatus, thus the PGA-PHA combination scaffold of Shum-Tim would appear to be able to be applied to the apparatus of Dunkelman as the vascular prosthesis. Dunkelman further states that cells may be seeded onto the vascular prosthesis scaffold, thus the combination of endothelial cells, fibroblasts and smooth muscle cells would appear to be able to be applied to the PGA-PHA scaffold in a manner as required by Shum-Tim, and then the seeded graft may be cultured under dynamic conditions so as to produce a vascular graft which may then be recovered and utilized in the implantation method of Shum-Tim et al. By carrying out the seeding and culturing of the vascular prosthesis of Shum-Tim et al within the apparatus of Dunkelman one would expect that the vascular graft would be pre-conditioned due to the dynamic conditioning, resulting in alignment of cells within the graft, which Dunkelman teaches is an improvement over static culture.

Therefore, the rationale for this conclusion of obviousness is that means for enhancing a particular method (the culture method of Shum-Tim et al) has been made part of the ordinary capabilities of one skilled in the art based upon the teachings of such improvements in other situations (specifically the perfusion system of Dunkelman et al). One of ordinary skill in the art would have been capable of applying the perfusion system of Dunkelman et al (the "enhancement") to the method of Shum-Tim et al (the "base method") and the results would have been predictable to one of ordinary skill in the art, specifically: successful development of a tissue engineered vascular graft which may be used in

subsequent transplantation procedures. See *KSR International Co. v Teleflex, Inc. 550 US___, ____, 82 USPQ2d 1385, 1395-97 (2007).*

Shum-Tim et al also differs from the instant invention in that they do not disclose one or more mitogenic factors in combination with one or more attractant factors, or one or more mitoattractant factors being provided in the inside of the support tube.

However, though Shum-Tim et al do not provide the details of the culture conditions in which the vascular graft is produced, it is submitted that it was known in the art that formation of a confluent endothelium prior to implantation was critical for patency of tissue engineered vascular grafts (See Mitchell et al, Pg. 59-60 "Endothelium"). It was further known that VEGF functions as a mitoattractant factor that serves to promote endothelialization of vascular grafts by promoting migration and proliferation of endothelial cells (See Hall et al, col. 19, ln 30-40).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art to perfuse the tissue engineered vascular graft of Shum-Tim et al, on the perfusion system of Dunkelman et al, with culture medium comprising VEGF in order to promote migration of the endothelial cells seeded within the scaffold to the luminal surface, and then to promote proliferation of the endothelial cells to form a confluent endothelium within the vascular graft. One would have had reasonable expectation of successfully including VEGF in the perfusion system because VEGF was readily available to the artisan (see, e.g. Hall et al), and its effects on endothelial cells were well documented (again, see Hall et al). The motivation to include VEGF in a culture medium which flows through the porous tubular support comes from the fact that development of a mature, confluent endothelium is critical for patency of the graft upon implantation (See Mitchell et al).

Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.